

### REMARKS

After entry of the amendments *supra*, claims 77, 83, 84, 88-95, 97-101, 103-115, 117, 122, 125-131, 133, 134, 137-146, 148-156, 159, 160, 163-168, and 170-191 are pending in this application. Claims 80, 81, 85, 86, 116, 118-121, 123, 135, 136, 147, 157, 158, 161, 162, and 169 have been canceled without prejudice, claims 77, 83, 84, 91, 93, 95, 97-99, 103, 106, 110-114, 122, 128, 134, 148-153, 156, 159, 160, 166, 168, 170, 171, and 175-177 have been amended, and new claims 178-191 have been added.

Claims 99, 114, 134 have been amended, and claim 169 has been canceled to address the Examiner's objections. Claims 80, 81, 85, 86, 116, 118-121, 123, 135, 136, 147, 157, 158, 161, and 162 have been canceled, and claims 77, 83, 84, 91, 93, 95, 97-99, 103, 106, 110-113, 122, 128, 134, 148-153, 156, 159, 160, 166, 168, 170, 171, and 175-177 have been amended solely to advance prosecution of the application. Support for new claims 178-191 may be found at, *inter alia*, page 13 lines 3-12; page 26 line 19 – page 27 line 7; page 26 lines 7-9; and Figure 20 of the specification. No new matter is believed to have been introduced by the amendments.

With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue any unclaimed subject matter in one or more continuation or divisional applications.

### Drawings

The Examiner has objected to the drawings for the reasons of record in the Action mailed 3/15/01. Applicants are submitting herewith a new set of formal drawings in order to comply with the objections raised by the Patent Office Draftsperson. No new matter is believed to have been introduced.

### Claim Objections

Claim 114 is objected to because "intravenously" is misspelled.

Claim 169 is objected to because it fails to further limit claim 156 which already requires that the complex has a diameter of less than about 400 nm.

Claims 99 and 34 are objected to as lacking a comma after the word “lipid”.

Applicants assume that the Examiner is objecting to claim 134, rather than claim 34, as there is no claim 34 currently pending. Claim 169 has been canceled, and claims 99, 114 and 134 have been amended to address the Examiner’s objections.

### **Double Patenting**

A. Claims 77, 89-94, 98-101, 104, 107-109, 139-141, 144-150, 156, 164-169, and 172-177 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-21 of U.S. Patent No. 5,795,587 (‘587) in view of Mack *et al.* Applicants respectfully traverse this rejection.

Applicants assert that the above-listed claims are non-obvious in view of the references cited by the Examiner. As an initial matter, Applicants note that claims 147 and 169 have been canceled without prejudice. Independent claims 77 and 156, and therefore their dependent claims, are directed to compositions and methods requiring a protamine *sulfate or chloride salt*. The Applicants note that claims 1-21 of the ‘587 patent recite a complex and method for producing nucleic acid/lipid/polycation complexes. These claims do not recite a protamine *sulfate or chloride salt*. Mack *et al.* do not teach or suggest the use of a protamine sulfate or chloride salt, either. Further, as is clearly described in the present application, inclusion of a protamine sulfate or chloride salt in the claimed complexes and methods unexpectedly and greatly increases transfection efficiency over nucleic acid/lipid/protamine *free base* (see, e.g., Example 10, page 45 line 16 – page 46 line 4). Neither claims 1-21 nor Mack *et al.* teach or suggest the unexpected and enhanced transfection efficiency of the claimed complexes and methods due to the inclusion of a protamine *sulfate or chloride salt*. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed compositions and methods obvious.

**B.** Claims 77, 104, 105, 113-117, 126-130, 134-136, and 151-153 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 6, 7, and 9-11 of U.S. Patent No. 5,795,587, in view of Mack *et al.* and Wu *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 116, 135 and 136 have been canceled without prejudice. Claims 77, 104, 105, 113-115, 117, 126-130, 134, and 151-153 are directed to compositions and methods requiring a protamine sulfate or chloride salt. As stated above, the Applicants assert that the instant claims reciting a protamine sulfate or chloride salt are not obvious in view of claims 6, 7, or 9-11 of the '587 patent and Mack *et al.* Wu *et al.* does not teach or suggest the use of a protamine sulfate or chloride salt, either. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed compositions and methods obvious.

**C.** Claims 95, 97, 98, 107, 131, 137, 138, 142, 143, 154, 155, 170, and 171 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 7, 9-11 of U.S. Patent No. 5,795,587, Mack *et al.* and Wu *et al.* as applied to claims 77, 104, 105, 113-117, 126-130, 134-136, and 151-153 above and further in view of Torchilin *et al.* Applicants respectfully traverse this rejection.

Claims 95, 97, 98, 107, 131, 137, 138, 142, 143, 154, 155, 170, and 171 are directed to compositions and methods requiring a protamine sulfate or chloride salt. As stated above, the Applicants assert that the instant claims reciting a protamine sulfate or chloride salt are not obvious in view of claims 6, 7, or 9-11 of the '587 patent, Mack *et al.*, and Wu *et al.* Torchilin *et al.* does not teach or suggest the use of a protamine sulfate or chloride salt, either. Therefore, the Applicants respectfully assert that the combination of these references do not render the claimed compositions and methods obvious.

**D.** Claims 77, 88-94, 98-101, 104, 105, 107-109, 113, 115-117, 125, 126, 130, 134-136, 151-153, 156, 163-169, and 172-177 are rejected under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,795,587, in view of Trubetskoy *et al.*, Hung *et al.*, and Kern *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 116, 135, 136 and 169 have been canceled without prejudice. Claims 77, 88-94, 98-101, 104, 105, 107-109, 113, 115, 117, 125, 126, 130, 134, 151-153, 156, 163-168, and 172-177 are directed to compositions and methods requiring a protamine sulfate or chloride salt. As stated above, the Applicants assert that the instant claims reciting a protamine sulfate or chloride salt are not obvious in view of claims 1-21 of the '587 patent. Neither Trubetskoy *et al.*, Hung *et al.*, or Kern *et al.* teaches or suggests compositions or methods comprising a protamine sulfate or chloride salt, either. Therefore, the Applicants respectfully assert that the combination of these references do not render the claimed compositions and methods obvious.

E. Claims 77, 80, 81, 83-86, 89-94, 98-101, 103, 104, 107-112, 139-141, 144-150, 156-162, 164-169, and 172-177 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-21 of U.S. Patent No. 5,795,587 in view of Mack *et al.* and Birnstiel *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 80, 81, 85, 86, 147, 157, 158, 161, 162 and 169 have been canceled without prejudice.

Claims 77, 83, 84, 89-94, 98-101, 103, 104, 107-112, 139-141, 144-146, 148-150 are directed to compositions and methods requiring complexes wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose. As noted above, claims 1-21 of the '587 patent recite a complex and method for producing nucleic acid/lipid/polycation complexes. These claims do not specifically recite complexes wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5%

dextrose. Applicants can not find any teaching in Mack *et al.* or Birnstiel *et al.* of compositions or methods comprising complexes, wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose.

Claims 156, 159, 160, 164-168, and 172-177 are directed to nucleic acid/lipid/protamine salt compositions requiring a complex having an average diameter of less than about 200 nm. Claims 1-21 of the '587 patent do not specifically recite complexes having an average diameter of less than about 200 nm. Applicants do not believe that the addition of Mack *et al.* and/or Birnstiel *et al.* renders the instant claims obvious. As noted by the Examiner, the DOGS/AP-PL:pCMVL complexes of Mack *et al.* have a mean diameter size ranging from about 280 to 560 nanometers. There is no further teaching or suggestion in the applied references to suggest that inclusion of protamine sulfate or chloride salt in a nucleic acid/lipid/protamine salt complex would result in complexes having an average diameter of less than about 200 nm, as claimed.

Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed compositions and methods obvious.

F. Claims 106 and 118-123 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 6, 7, and 9-11 of U.S. Patent No. 5,795,587, in view of Mack *et al.* and Wu *et al.* as applied to claims 77, 104, 105, 113-117, 126-130, 134-136, and 151-153 above, and further in view of Birnstiel *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 118-121 and 123 have been canceled without prejudice. Claims 106 and 122 are directed to methods requiring complexes wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose. As noted above, neither claims 1-21 of the '587 patent nor Mack *et al.* disclose or suggest compositions or methods comprising complexes, wherein the diameter of the stored complex does

not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose. Wu *et al.* further does not suggest or disclose compositions or methods comprising complexes, wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed methods obvious.

In light of the above remarks, Applicants respectfully requests withdrawal of the above listed obviousness-type double patenting rejections (A-F).

#### **Rejections under 35 U.S.C. § 102**

Claims 77, 89, 93, 94, 98-100, 104, 107-109, 139-141, 144-146, 156, 164, 168, 169, and 172-177 are rejected under 102(b) as being allegedly anticipated by Mack *et al.* Applicants respectfully traverse this rejection.

Applicants note that claim 169 has been canceled without prejudice. Independent claims 77 and 156, and therefore their dependent claims, are directed to compositions and methods requiring a protamine sulfate or chloride salt. Mack *et al.* discloses, as summarized by the Examiner, methods pertaining to complexes comprising asialoglycoprotein-modified polylysine, plasmid DNA and cationic lipids, where the polylysine is covalently modified, attaching asialoglycoprotein.

Applicants cannot find any teaching in Mack *et al.* directed to the inclusion of protamine sulfate or chloride salts. The experimental section of the reference discloses only the use of poly-L-lysine. As such, the reference does not teach each limitation of the independent claims 77 and 156 and therefore does not anticipate claims 77 and 156, or their respective dependent claims.

In light of the above remarks, Applicants respectfully request withdrawal of the rejection of claims 77, 89, 93, 94, 98-100, 104, 107-109, 139-141, 144-146, 156, 164, 168, and 172-177 under 35 U.S.C. §102.

**Rejections under 35 U.S.C. § 103**

While the Applicants do not agree with the basic assertions put forth by the Examiner with respect to the rejections under 35 U.S.C. 103, in the interests of efficiently moving the prosecution of the present application forward, Applicants provide the comments appearing below.

A. Claims 77, 91, 98, 104, 107-109, 139-141, 144-146, 156, 166 and 172-177 are rejected under 103(a) as being unpatentable over Mack *et al.* in view of Curiel *et al.* Applicants respectfully traverse this rejection.

Claims 77, 91, 98, 104, 107-109, 139-141, 144-146, 156, 166 and 172-177 are directed to compositions and methods requiring a protamine sulfate or chloride salt. As stated above, there is no teaching or suggestion in Mack *et al.* of compositions or methods comprising a protamine sulfate or chloride salt. There is further no teaching or suggestion in Curiel *et al.* of compositions or methods comprising a protamine sulfate or chloride salt, either. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed compositions and methods obvious.

B. Claims 77, 89, 93, 94, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177 are rejected under 103(a) as being unpatentable over Wu *et al.* in view of Mack *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 116, 135, 136 and 169 have been canceled without prejudice. Claims 77, 89, 93, 94, 98-100, 104, 105, 107-109, 113-115, 117, 126, 130, 134, 139-141, 144-146, 151-153, 156, 164, 168, and 172-177 are directed to compositions and

methods requiring a protamine sulfate or chloride salt. As stated above, there is no teaching or suggestion in Mack *et al.* or Wu *et al.* of compositions or methods comprising a protamine sulfate or chloride salt. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed compositions and methods obvious.

C. Claims 113, 128, 131, 136, and 147-153 are rejected under 103(a) as being unpatentable over Wu *et al.* and Mack *et al.* as applied to claims 77, 89, 93, 84, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, 172-177 above, and further in view of Curiel *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 136 and 147 have been canceled without prejudice. Claims 113, 128, 131, and 148-153 are directed to methods requiring a protamine sulfate or chloride salt. As stated above, there is no teaching or suggestion in Mack *et al.*, Wu *et al.*, or Curiel *et al.* of compositions or methods comprising a protamine sulfate or chloride salt. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed methods obvious.

D. Claims 77, 88, 89, 93, 94, 98-100, 104, 105, 113, 115-117, 125, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 163, 164, 168, 169, and 172-177 are rejected under 103(a) as being unpatentable over Hung *et al.*, in view of Trubetskoy *et al.*, Mack, and Kern *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 116, 135, 136 and 169 have been canceled without prejudice. Claims 77, 88, 89, 93, 94, 98-100, 104, 105, 113, 115, 117, 125, 126, 130, 134, 139-141, 144-146, 151-153, 156, 163, 164, 168, and 172-177 are directed to compositions and methods requiring a protamine sulfate or chloride salt. As stated above, there is no teaching or suggestion in Hung *et al.*, Trubetskoy *et al.*, Mack *et al.*, or Kern *et al.* of compositions or methods comprising a protamine sulfate or chloride salt. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed compositions and methods obvious.



E. Claims 90, 92, 101, 106, 127, 129, 165, 167, and 168 are rejected under 103(a) as being unpatentable over Wu and Mack as applied to claims 77, 89, 93, 94, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177, above and further in view of Trubetskoy *et al.*, and Harris *et al.* Applicants respectfully traverse this rejection.

Claims 90, 92, 101, 106, 127, 129, 165, 167, and 168 are directed to compositions and methods requiring a protamine sulfate or chloride salt. As stated above, there is no teaching or suggestion in Wu *et al.*, Mack *et al.*, or Trubetskoy *et al.* of compositions or methods comprising a protamine sulfate or chloride salt. Harris *et al.* does not teach compositions or methods comprising a protamine sulfate or chloride salt, either. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed compositions and methods obvious.

F. Claims 95, 97, 131, 133, 137, 138, 142, 143, 147-150, 154, 155, 170, and 171 are rejected under 103(a) as being unpatentable over Wu and Mack as applied to claims 77, 89, 93, 94, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177, and further in view of Torchilin *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claim 147 has been canceled without prejudice. Claims 95, 97, 131, 133, 137, 138, 142, 143, 148-150, 154, 155, 170, and 171 are directed to compositions and methods requiring a protamine sulfate or chloride salt. As stated above, there is no teaching or suggestion in Wu *et al.*, Mack *et al.*, or Torchilin *et al.* of compositions or methods comprising a protamine sulfate or chloride salt. Therefore, the Applicants respectfully assert that the combination of these references does not render the claimed compositions and methods obvious.

G. Claims 77, 80, 81, 83-86, 98, 103, 110-112, and 156-162 are rejected under 103(a) as being unpatentable over Mack *et al.* in view of Birnstiel *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 80, 81, 85, 86, 157, 158, 161 and 162 have been canceled without prejudice.

Claims 77, 83, 84, 98, 103, and 110-112 are directed to compositions and methods requiring complexes wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose. As noted above, Applicants can not find any teaching in Mack *et al.* or Birnstiel *et al.* of compositions or methods comprising complexes, wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose.

Claims 156 and 160 are directed to nucleic acid/lipid/protamine salt compositions requiring a complex having an average diameter of less than about 200 nm. Mack *et al.* discloses, as summarized by the Examiner, methods pertaining to complexes comprising asialoglycoprotein-modified polylysine, plasmid DNA and cationic lipids, where the polylysine is covalently modified, attaching asialoglycoprotein. There is no teaching or suggestion in Mack *et al.* of compositions comprising a protamine, and in particular, a protamine sulfate or chloride salt. Birnstiel relates to compositions comprising an internalizing factor/bonding factor conjugate and a nucleic acid. As noted above, Applicants do not believe that the combination of Mack *et al.* and Birnstiel *et al.* renders the claims obvious. Neither Mack *et al.* nor Birnstiel *et al.* disclose nucleic acid/lipid/protamine salt complexes having an average diameter of less than about 200 nm. As noted by the Examiner, the DOGS/AP-PL:pCMVL complexes of Mack *et al.* have a mean diameter size ranging from about 280 to 560 nanometers. There is no teaching or suggestion in the applied references to suggest that inclusion of protamine sulfate or chloride salt in a nucleic acid/lipid/protamine salt complex would result in complexes having an average diameter of less than about 200 nm, as claimed.

Therefore, the Applicants respectfully assert that the combination of these references do not render the claimed compositions and methods obvious.

**H.** Claims 106 and 118-123 are rejected under 103(a) as being unpatentable over Mack *et al.* and Wu *et al.* as applied to claims 77, 89, 93, 94, 98-100, 104, 105, 107-109, 113-117, 126, 130, 134-136, 139-141, 144-146, 151-153, 156, 164, 168, 169, and 172-177, and further in view of Birnstiel *et al.* Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that claims 118-121 and 123 have been canceled without prejudice. Claims 106 and 122 are directed to methods requiring complexes wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose. As noted above, neither Mack *et al.*, Birnstiel *et al.* nor Wu *et al.*, alone or in combination, discloses or suggests compositions or methods comprising complexes, wherein the diameter of the stored complex does not increase by more than 100% over the diameter of the complex as determined at the time the complex was purified, after 4 months in storage in 5% dextrose. Therefore, Applicants respectfully asserts that the combination of these references does not render the claimed methods obvious.

In light of the above remarks, Applicants respectfully request withdrawal of the above listed rejections (A-H) under 35 U.S.C. §103(a).

### CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.226272002201. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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